

FDUR - floxuridine injection, powder, lyophilized, for solution
Mayne Pharma (USA) Inc.

STERILE FDUR

(brand of floxuridine)

FOR INTRA-ARTERIAL INFUSION ONLY

R_x only

WARNING

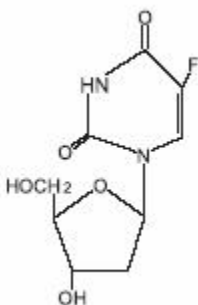
It is recommended that FUDR be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and intra-arterial drug therapy and is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, all patients should be hospitalized for initiation of the first course of therapy.

DESCRIPTION

Sterile FUDR (floxuridine), an antineoplastic antimetabolite, is available as a sterile, nonpyrogenic, lyophilized powder for reconstitution. Each vial contains 500 mg of floxuridine which is to be reconstituted with 5 mL of sterile Water for Injection. An appropriate amount of reconstituted solution is then diluted with a parenteral solution for intra-arterial infusion (see **DOSAGE AND ADMINISTRATION** section).

Floxuridine is a fluorinated pyrimidine. Chemically, floxuridine is 2'-deoxy-5-fluorouridine with an empirical formula of C₉H₁₁FN₂O₅. It is a white to off-white odorless solid which is freely soluble in water.

The 2% aqueous solution has a pH of between 4.0 and 5.5. The molecular weight of floxuridine is 246.19 and the structural formula is:



CLINICAL PHARMACOLOGY

When FUDR is given by rapid intra-arterial injection it is apparently rapidly catabolized to 5-fluorouracil. Thus, rapid injection of FUDR produces the same toxic and antimetabolic effects as does 5-fluorouracil. The primary effect is to interfere with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibit the formation of ribonucleic acid (RNA). However, when FUDR is given by continuous intra-arterial infusion its direct anabolism to FUDR-monophosphate is enhanced, thus increasing the inhibition of DNA. Floxuridine is metabolized in the liver. The drug is excreted intact and as urea, fluorouracil, a-fluoro-bureidopropionic acid, dihydrofluorouracil, a-fluoro-b-guanidopropionic acid and a-fluoro-b-alanine in the urine; it is also expired as respiratory carbon dioxide. Pharmacokinetic data on intra-arterial infusion of FUDR are not available.

INDICATIONS AND USAGE

FUDR is effective in the palliative management of gastrointestinal adenocarcinoma metastatic to the liver, when given by continuous regional intra-arterial infusion in carefully selected patients who are considered incurable by surgery or other means. Patients with known disease extending beyond an area capable of infusion via a single artery should, except in unusual circumstances, be considered for systemic therapy with other chemotherapeutic agents.

CONTRAINDICATIONS

FUDR therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections.

WARNINGS

BECAUSE OF THE POSSIBILITY OF SEVERE TOXIC REACTIONS, ALL PATIENTS SHOULD BE HOSPITALIZED FOR THE FIRST COURSE OF THERAPY.

FUDR should be used with extreme caution in poor risk patients with impaired hepatic or renal function or a history of high-dose pelvic irradiation or previous use of alkylating agents. The drug is not intended as an adjuvant to surgery.

FUDR may cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in the chick embryo, mouse (at doses of 2.5 to 100 mg/kg) and rat (at doses of 75 to 150 mg/kg). Malformations included cleft palates; skeletal defects; and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 4.2 to 125 times the recommended human therapeutic dose.

There are no adequate and well-controlled studies with FUDR in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Combination Therapy

Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of FUDR.

PRECAUTIONS

General

Sterile FUDR is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of FUDR despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

Myocardial ischemia

Stomatitis or esophagopharyngitis, at the first visible sign

Leukopenia (WBC under 3500) or a rapidly falling white blood count

Vomiting, intractable

Diarrhea, frequent bowel movements or watery stools

Gastrointestinal ulceration and bleeding

Thrombocytopenia (platelets under 100,000)

Hemorrhage from any site

Information for Patients

Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

Laboratory Tests

Careful monitoring of the white blood count and platelet count is recommended.

Drug Interactions

See **WARNINGS** section.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of floxuridine have not been conducted. On the basis of the available data, no evaluation can be made of the carcinogenic risk of FUDR to humans.

Mutagenesis

Oncogenic transformation of fibroblasts from mouse embryo has been induced in vitro by FUDR, but the relationship between oncogenicity and mutagenicity is not clear. Floxuridine has also been shown to be mutagenic in human leukocytes in vitro and in the Drosophila test system. In addition, 5-fluorouracil, to which floxuridine is catabolized when given by intra-arterial injection, has been shown to be mutagenic in in vitro tests.

Impairment of Fertility

The effects of floxuridine on fertility and general reproductive performance have not been studied in animals. However, because floxuridine is catabolized to 5-fluorouracil, it should be noted the 5-fluorouracil has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats at doses of 125 or 250 mg/kg, administered intraperitoneally.

Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. In female rats, fluorouracil, administered intraperitoneally at doses of 25 or 50 mg/kg during the preovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and postimplantation embryos, increased the incidence of

preimplantation lethality and induced chromosomal anomalies in these embryos. Compounds such as FUDR, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

Pregnancy:

Teratogenic Effects:

Pregnancy Category D:

(See **WARNINGS** section). Floxuridine has been shown to be teratogenic in the chick embryo, mouse (at doses of 2.5 to 100 mg/kg) and rat (at doses of 75 to 150 mg/kg). Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 4.2 to 125 times the recommended human therapeutic dose.

There are no adequate and well-controlled studies with FUDR in pregnant women. While there is no evidence of teratogenicity in humans due to FUDR, it should be kept in mind that other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. FUDR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Floxuridine has not been studied in animals for its effects on peri- and postnatal development. However, compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Nursing Mothers:

It is not known whether FUDR is excreted in human milk. Because FUDR inhibits DNA and RNA synthesis, mothers should not nurse while receiving this drug.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to the arterial infusion of FUDR are generally related to the procedural complications of regional arterial infusion. The more common adverse reactions to the drug are nausea, vomiting, diarrhea, enteritis, stomatitis and localized erythema. The more common laboratory abnormalities are anemia, leukopenia, thrombocytopenia and elevations of alkaline phosphatase, serum transaminase, serum bilirubin and lactic dehydrogenase.

Other adverse reactions are:

Gastrointestinal: duodenal ulcer, duodenitis, gastritis, bleeding, gastroenteritis, glossitis, pharyngitis, anorexia, cramps, abdominal pain; possible intra- and extrahepatic biliary sclerosis, as well as acalculous cholecystitis.

Dermatologic: alopecia, dermatitis, nonspecific skin toxicity, rash.

Cardiovascular: myocardial ischemia.

Miscellaneous Clinical Reactions: fever, lethargy, malaise, weakness.

Laboratory Abnormalities: BSP, prothrombin, total proteins, sedimentation rate and thrombopenia.

Procedural Complications of Regional Arterial Infusion: arterial aneurysm; arterial ischemia; arterial thrombosis; embolism; fibromyositis; thrombophlebitis; hepatic necrosis; abscesses; infection at catheter site; bleeding at catheter site; catheter blocked, displaced or leaking.

The following adverse reactions have not been reported with FUDR but have been noted following the administration of 5-fluorouracil. While the possibility of these occurring following FUDR therapy is remote because of its regional administration, one should be alert for these reactions following the administration of FUDR because of the pharmacological similarity of these two drugs: pancytopenia, agranulocytosis, myocardial ischemia, angina, anaphylaxis, generalized allergic reactions, acute cerebellar syndrome, nystagmus, headache, dry skin, fissuring, photosensitivity, pruritic maculopapular rash, increased pigmentation of the skin, vein pigmentation, lacrimal duct stenosis, visual changes, lacrimation, photophobia, disorientation, confusion, euphoria, epistaxis and nail changes, including loss of nails.

OVERDOSAGE

The possibility of overdosage with FUDR is unlikely in view of the mode of administration. Nevertheless, the anticipated manifestations would be nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdosage of FUDR should be monitored hematologically for at least 4 weeks. Should abnormalities appear, appropriate therapy should be utilized. The acute intravenous toxicity of floxuridine is as follows:

| Species | LD ₅₀ |
|---------|------------------|
| | (mg/kg ± S.E.) |
| Mouse | 880 ± 51 |
| Rat | 670 ± 73 |
| Rabbit | 94 ± 19.6 |
| Dog | 157 ± 46 |

DOSAGE AND ADMINISTRATION

Each vial must be reconstituted with 5 mL of sterile Water for Injection to yield a solution containing approximately 100 mg of floxuridine /mL. The calculated daily dose(s) of the drug is then diluted with 5% dextrose or 0.9% sodium chloride injection to a volume appropriate for the infusion apparatus to be used. The administration of FUDR is best achieved with the use of an appropriate pump to overcome pressure in large arteries and to ensure a uniform rate of infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The recommended therapeutic dosage schedule of FUDR by continuous arterial infusion is 0.1 to 0.6 mg/kg/day. The higher dosage ranges (0.4 mg to 0.6 mg) are usually employed for hepatic artery infusion because the liver metabolizes the drug, thus reducing the potential for systemic toxicity. Therapy can be given until adverse reactions appear (see **PRECAUTIONS** section). When these side effects have subsided, therapy may be resumed. The patient should be maintained on therapy as long as response to FUDR continues. Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁶ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

NDC 61703-331-09 - 500 mg Sterile FUDR (floxuridine) powder in a 5 mL vial packaged individually.

This is to be reconstituted with 5 mL sterile water for injection. The sterile powder should be stored at 15°C to 30°C (59°F to 86°F). Reconstituted vials should be stored under refrigeration 2°C to 8°C (36°F to 46°F) for not more than 2 weeks.

REFERENCES

1. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC, US Government Printing Office NIH publication 83-2621.
2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA. Mar 15,1985, 253:1590-1592.
3. National Study Commission on Cytotoxic Exposure: Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J Aust. Apr 30 , 1983, 1:426-428.
5. Jones, RB, Frank R, Mass T: Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA. Sept-Oct, 1983, 33:258-263.
6. ASHP American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs in Hospitals. Am J. Hosp Pharm Jan, 1985, 42:131-137.

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